OFFICE OF NAVAL RESEARCH

ANNUAL PROGRESS REPORT

and

PROPOSAL FOR RENEWAL OF CONTRACT

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CONTRACTOR: Yale University

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TITLE OF PROJECT: NEUROLOGICAL MECHANISMS IN EPILEPSY AND IN GROUP BEHAVIOR
Objectives: a) Study in awake animals of neurological mechanisms involved in the onset, spread and clinical manifestations of epilepsy.

b) Influence of cerebral stimulation on group behavior of animals recorded by time lapse photography.

ABSTRACT OF RESULTS

A. Since Start of Project

Summary of published work in 1954 follows:

1. LEARNING MOTIVATED BY ELECTRICAL STIMULATION OF THE BRAIN. Permanent multilead needle electrodes were implanted within the brains of seven experimental and four control cats to determine whether the emotional disturbance induced by electrical stimulation of specific structures could be used to motivate learning. A 'fear-like' reaction could be elicited from 3 regions: a) the superior part of the tectal area in the neighborhood of the spinothalamic tract; b) the lateral nuclear mass of the thalamus; and c) the inferomedial part of the hippocampal gyrus. Stimulation of certain other regions of the brain, including the sensorimotor area, did not elicit this fear-like reaction. The fear-like reaction elicited by stimulation in these regions had all the drive properties of a true emotion: a) it could be used to establish a conditioned response; b) it could motivate the trial and error learning and performance of an instrumental response; c) it could be used to condition an emotional disturbance to a distinctive compartment, and after this, during trials without any further stimulation, the animals would learn to escape from that compartment; d) it could serve as a punishment to teach hungry animals to avoid food. In similar tests on control cats, stimulation with higher voltages at other points in the sensorimotor area elicited stronger motor responses, but had much less, if any motivational effect.

2. A study of FUNCTIONAL CORRELATION BETWEEN MOTOR CORTEX AND CEREBELLUM. Doctoral thesis by Arnold Schulman.

B. During Current Report Period

Summary of published work, papers accepted for publications, and work in progress follows:

1. CEREBRAL STRUCTURES INVOLVED IN TRANSMISSION AND ELABORATION OF NOXIOUS STIMULATION. A peripheral noxious stimulus evokes in the monkey a typical pattern of response which includes defensive and offensive movements, vocalization, and autonomic manifestations. Conditioning is possible with such stimulation.

The aim of this investigation has been to study which areas of the brain could produce a similar pattern. Monkeys and a smaller number of cats were studied for about a two-month period each by means of permanently implanted multilead electrodes.

Electrical stimulation of the lateral part of the tegmentum, the central gray, the posteroventral nucleus of the thalamus, the crus of the fornix and the posterior part of the hippocampus elicited the typical pattern. Stimulation of the other areas of the brain, including the sensorimotor cortex, did not evoke these reactions.

A technique for chemical stimulation of the brain by remote control is described. Injection of acetylcholine into the tegmental part of the pons did not evoke the typical pattern.

In the cat, electrical stimulation of the tectal area induced fighting against control animals, showing that the offensive reaction was purposive and well oriented.

The fact that a similar pattern was induced by stimulation of the above mentioned structures suggests a close functional relationship. The so-called sensory cortex would have a less important role than the thalamus and hippocampus in nociceptive sensory integrations.

2. INFLUENCE OF VARIOUS CO_2 CONCENTRATIONS ON ELECTRICAL ACTIVITY AND EXCITABILITY OF THE BRAIN IN THE WAKING MONKEY. In monkeys, multilead electrodes were permanently implanted for a period of 1-3 months in order to study the action of 5%, 10%, 15% and 30% concentrations of CO_2 in the air upon the brain.

The following areas were studied; motor cortex, occipital cortex, centrum medianum of the thalamus, hypothalamus, and reticular substance. After 10 min. exposure to 10%, 15% or 30% CO_2, there was a generalized slowing down and decrease in amplitude in monopolar recording of all the areas, with the exception of the hypothalamus, which seemed to be less affected. With 10% and 15% CO_2, bipolar recordings of the hypothalamus and reticular substance showed increased occurrence of runs of 5-7 cps, of higher amplitude. This phenomenon was also seen when the animals were exposed to 5% CO_2. With 30% CO_2 there was an initial period of increased number of 5-7 cps, followed by a gradual disappearance of this activity. In some animals after 18 min. of exposure to 15% CO_2, the reticular substance and later the hypothalamus showed bursts of 3/second waves of 300 microvolts. These bursts were rather localized and only from time to time spread to more superficial structures. Threshold of electrical stimulation of the hypothalamus and reticular formation decreased under 10%, 15% and 30% CO_2. Thresholds in other areas of the brain showed variable changes.

3. CEREBRO-CEREBELLAR CORRELATIONS IN THE AWAKE CAT. In 40 cats, multilead 'plate' and 'needle' electrodes were permanently implanted in the cerebral motor area and ansiform and paramedian lobules of the cerebellum. Movements elicited from the cerebellum at threshold were well co-ordinated, discrete responses almost indistinguishable from those from the cerebral motor area. With higher intensities, rebound reactions occurred. Representation of movements was diffuse in the neocerebellar hemispheres. Equilibrator changes were evoked by cerebellar stimulation, and lasted 3-5 min. after stimulation. When both cerebral motor area and cerebellum were simultaneously stimulated, motor effects from each appeared to retain their distinctive characteristics, with co-ordinated interactions. Simultaneous stimulation of cerebral motor area and cerebellum at varying percentages (25-90%) of cerebellar threshold exerted little or no effect upon excitability of the cerebral motor area. Destruction of anterior and

posterior sigmoidal gyri or the entire frontal pole altered neither threshold nor character of movements evoked from the cerebellum. Destruction of the cerebellum resulted in severe postural defects without changing the character of movements evoked from the cerebral motor area.

4. EVALUATION OF PERMANENT IMPLANTATION OF ELECTRODES WITHIN THE BRAIN. The paper deals with technical details and critical evaluations of implanting electrodes within the brain of 75 cats and 63 monkeys for a one to fourteen month period. In both groups, no operatory accidents occurred, and no deficits were produced by electrode insertion.

After several months of implantation, plate electrodes produced a small impression on the brain surface without histological alteration of the neurons. Damage of the brain resulting from needle electrodes was generally less than 1 mm. in diameter. Infections were rare. Electrocoagulation was more hazardous.

Prolonged electrical stimulation of the brain did not cause any detectable local histological changes.

Cerebral stimulation was possible in cats and monkeys which had freedom of movement. This permitted studies concerning behavior, sensory phenomena, correlations between clinical manifestations and electrical activity of the brain, and also psychological testing of the animals.

Patterns of response evoked by electrical stimulation proved to be typical for each point, and reliable through time.

Thresholds of electrical stimulation proved to be rather constant throughout the months of observation.

"Spontaneous" electrical activity and patterns of evoked post discharges recorded by means of implanted electrodes were similar in recordings taken with weeks or months of interval.

It may be concluded that the presence of electrodes disturbs the brain activity very little, or at least, that the experimental conditions do not change

during the period of observation.

5. ELECTRICAL STIMULATION OF MONKEY BRAIN WITH VARIOUS FREQUENCIES AND PULSE DURATIONS. Effects of altering the duration and frequency of pulses upon the threshold of motor and autonomic responses produced by electrical stimulation of different cortical and subcortical areas of the brain were studied in unanesthetized monkeys with permanently implanted electrodes. Pulses of 0.01-5.0 msec. duration, and frequency ranges of 10-5000 cycles/sec. were used. Voltage and current of stimuli passing through the animal were simultaneously monitored and measured by a dual channel cathode-ray oscilloscope. The following conclusions are derived from the experimental results: 1) Voltage/current ratio was the same before and after the implantation of electrodes, indicating that prolonged contact with organic tissue does not significantly change the electrical properties of the electrode. 2) Pulse durations of 0.1-0.5 msec. were generally most effective in evoking both motor and autonomic responses. 3) The lowest threshold for both motor and autonomic responses occurred at frequencies of 100-250 cycles/sec. At higher frequencies a sharper increase in threshold values was observed in the case of autonomic responses. In most of the areas studied variation in frequency of stimuli resulted in change of the type of evoked motor responses. At low frequencies (up to 30 cycles/sec.) single contractions followed the rate of stimuli; at higher frequencies (60-500) smooth movements occurred; at very high frequencies (1000-5000) quick, jerky movements at onset of stimulation were observed. Similar fundamental changes, and at approximately the same critical frequencies, were obtained from different, widely separated areas of the gray and the white matter of both cortical and subcortical areas of the brain.

6. EVOKING CONDITIONED FEAR BY ELECTRICAL STIMULATION OF SUBCORTICAL STRUCTURES IN THE MONKEY BRAIN. An assembly containing six electrodes was implanted in mesencephalic, diencephalic, and rhinencephalic structures in the

brains of 10 monkeys (macaca mulatta), which had been trained to avoid shock to the feet. Electrical stimulation of some structures evoked a response identical to the response performed by the animal to avoid shock; of other structures, an inhibitory response; of other structures, motor effect; and of some structures no apparent response.

Stimulation of the following structures elicited the conditioned fear response: medial nucleus of the amygdala and adjacent tissue in rhinal fissure, trigeminal nerve at the Gasserian ganglion, rostral part of the pons, medial part of the mesencephalon in the vicinity of the central gray, nucleus ventralis posteromedialis, external part of the nucleus ventralis posterolateralis of the thalamus, and external medullary lamina of the pallidum.

Electrical stimulation of the following structures did not evoke the avoidance response: sensorimotor cortex, sensorimotor pathways, nucleus ventralis lateralis of the thalamus, pulvinar of the thalamus, substantia nigra, part of the tegmentum inferior to the central gray, anterior hippocampus, posterior portions of the amygdaloid nucleus, and the putamen.

A great variety of motor effects affecting head, eyes, face, forelimbs, hindlimbs and also the tail were evoked by stimulation. In some instances responses were inhibited by stimulation.

The results suggest that fear may be induced by electrical stimulation of some structures, not others. The structures from which fear was elicited appear to be related to the limbic system. These results are interpreted as indicating that electrical stimulation of some subcortical structures elicits fear responses which may be adapted to external circumstances.

7. THE EFFECT ON DELAYED-ALTERNATION TEST PERFORMANCE OF STIMULATING OR DESTROYING ELECTRICALLY STRUCTURES WITHIN THE FRONTAL LOBES OF THE MONKEYS BRAIN. Multilead electrodes were implanted bilaterally within the frontal lobes

of fourteen monkeys (Macaca mulatta) which had been trained in delayed-alternation and visual discrimination problems. The effect on the performance of these tests was observed while structures within the frontal lobe were being electrically stimulated through the electrode leads. Later, the effect on the performance of these tests was observed during electrocoagulation of these structures in some animals, and after electrocoagulation in others. The structures stimulated and electrocoagulated were determined by microscopic examination of stained sections.

Impairment of the delayed-alternation test but not other visual discrimination test resulted from stimulation of small areas in the head of the caudate nucleus, and not from any other structure.

Electrocoagulation of tissue in the head of the caudate nucleus, but not in any other structure, also impaired delayed alternation performance.

Changes in activity, and gastrointestinal disturbances followed stimulation of caudate nucleus and putamen. Electrocoagulation of tissue in the caudate and in the putamen resulted in gastrointestinal disturbances which lasted for a few days, and in hyperactivity which persisted throughout the rest of the life of the animal.

The results of this study thus suggest that the delayed alternation deficit changes in activity, and gastrointestinal disturbances, which frequently follow prefrontal lobotomy or ablation of frontal cortex and which are usually ascribed to damage to the cortical projections from the thalamus, are due instead to damage to the corpus striatum, particularly the caudate nucleus and its cortical projections.

The complicated relationships between the behavioral affects of stimulation and coagulation preclude an explanation in terms of any one cerebral process.

8. MOTOR REPRESENTATION IN THE FRONTAL SULCI OF THE CAT. Cortex hidden within enclosed portions of the sulci cruciatus, coronalis and presylvius,

has been stimulated electrically in twenty cats under Dial anesthesia by means of bipolar concentric electrodes directed stereotaxically so as to penetrate the frontal lobe millimeter by millimeter.

The hidden cortex forming the walls of these sulci in each hemisphere has a combined extent of more than three hundred square millimeters, an area comparable to the surface extent of the frontal lobe of the cat. Throughout subsurface cortex there is an important and essentially continuous "sensorimotor" region from which discrete somatic motor movements may be evoked.

Stimulation of the cortex within the cruciate sulcus yields movements of the contralateral hindlimb, trunk and tail. There is a small region of forelimb representation in the anterior part of this sulcus. Forelimb responses are also elicitable from the anterior part of sulcus coronalis. Within the sulcus presylvius there is an extensive motor representation of the anterior half of the animal: forelimbs near the top, head and neck movements, face, vibrissae, eyelid and eye movements, jaw, tongue, pupillary and respiratory responses as the orbital surface is reached. There are differences in representation within the opposing surfaces of each of these three sulci and each bank appears to provide a series of motor representations which are continuous with those encountered on stimulation of the surface gyri.

9. ELECTROENCEPHALOGRAPHY OF THE DEEPER CELL MASSES OF THE BRAIN. This is a chapter in the book entitled "Atlas of the Human Brain" by P. Bailey and Schaltenbrandt to be published simultaneously in English and German.

10. CONVULSIVE ACTIVITY EVOKED BY CEREBRAL STIMULATION IN THE AWAKE MONKEY. Surface and depth leads, up to 40, were implanted in the brain of 22 monkeys (Macaca mulatta) for 2-7 months. In the awake animal thresholds for evoking electrical and motor convulsive manifestations were determined, and electrical activity was recorded through 14 channels. Correlations between

electrical and motor manifestations were studied in the following structures: frontal, premotor, motor, temporal and occipital cortex; cingulate gyrus; septal area; amygdaloid nucleus; hippocampus; fornix; basal ganglia; thalamic nuclei; subthalamus; hypothalamus; brain stem reticular formation. The motor cortex had the lowest convulsive threshold, convulsive movements were usually localized and electrical after-discharges spread over a wide area. The premotor cortex had somewhat higher thresholds with more motor spreading. The frontal cortex had still higher convulsive thresholds and the occipital cortex had the highest. Their electrical after-discharges usually remained localized. The duration of after-discharges was longest from motor and premotor cortex, shorter from frontal, and shortest from occipital cortex. Of the deep structures, the hippocampus had the lowest convulsive threshold. Stimulation of the cingulate gyrus with intensities insufficient to produce an after-discharge from this area fired the contralsteral hippocampus to discharge for a considerable period. Discharges in both temporal tips were produced by septal stimulation. Electrical after-discharges produced from various thalamic nuclei had higher thresholds than hippocampal and septal discharges. Even with the highest intensities employed convulsive movements were not evoked by stimulation of the caudate nuclei. Significant lowering of convulsive threshold and increased tendency toward spreading could be observed when an area was repeatedly stimulated for long periods with intensities producing convulsive after-discharges.

11. LASTING EFFECTS ON BEHAVIOR EVOKED BY CEREBRAL STIMULATION OF THE CAT. Previous studies have shown that it is possible to produce lasting increase of food intake after stimulation of the lateral hypothalamus. In the present paper an attempt was made to learn whether electrical stimulation of the brain could produce plastic changes reflected in group behavior of cats. Male and female cats were grouped in colonies of 4 to 8 animals, and their behavior continuously recorded for 10 hours daily by a time lapse camera which took one

picture every 9 seconds. Films were later analyzed according to different patterns of behavior, selected after previous experience. Data concerning frequencies and time spent in each pattern were tabulated for each animal, in tables which bring outstanding features readily to the eye and provide data for statistical treatment. Needle electrodes were permanently implanted within the brain of several males of the colony. Later, intermittent electrical stimulation was applied to each animal, half a second every 5 seconds for one hour daily, for 1-2 weeks. Stimulation through leads aimed to the amygdaloid complex produced in some cats considerable increase in frequency and in time spent nuzzling, sniffing, licking, rubbing, etc., and also an increase in "playful" activity. These effects were present throughout the whole day and lasted for several days after stimulation was discontinued. Negative results were observed after stimulation of other cerebral structures.

12. WORK IN PROGRESS. 25 monkeys with implanted electrodes within the brain for several months, have been studied and considerable material dealing with epileptic mechanisms has been accummulated.

Several papers are being prepared for future publication.

PLANS FOR FUTURE:

Immediate

1. Study of epileptic mechanisms will continue and will mainly deal with occipital cortex, motor cortex, premotor area, frontal lobes, limbic system, thalamus and brain stem.

2. [redacted] the method of implanted electrodes will be used to study the site of action of drugs which act on the central nervous system, mainly stimulants and antiepileptics.

3. Study of group behavior in animals with implanted electrodes will be expanded.

Long Range

Fulfillment of the plan mentioned above will keep us busy a long time. The most important addition is the study of group behavior in social colonies of cats and monkeys using time lapse photography recordings. With this method, objective and permanent records of the behavior of animals may be obtained. This material may be analyzed statistically. The method will be used to study the modifications of behavior induced by electrical stimulations of different cerebral structures through implanted electrodes.

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